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19. ABSTRACT (Continue on reverse if necessary and identify by block number) These studies have been part of an ongoing research program on the ability of certain nutrients to affect the production of their neurotransmitter products, and thereby to affect behaviors and other brain functions (e.g., control of blood pressure). The studies have focussed on the amino acid tyrosine - which is converted, in neurons or chromaffin cells, to dopamine, norepinephrine, and epinephrine. The effect of supplemental tyrosine on brain dopamine release has now been shown directly, using the new technique of <u>in vivo</u> microdialysis. Hemorrhage, per se, has been shown to raise neuronal tyrosine levels, probably reflecting a protective mechanism to sustain blood pressure. Adenosine and the amino acid alanine have now also been shown to modulate blood pressure - and adenosine to mediate some of the fall in blood pressure caused by hemorrhage. Various dipeptides & diketopiperazines have been shown to enhance dopamine release, either by providing tyrosine or by direct actions. In related studies, we have examined the interactions of dietary carbohydrates (which, acting via insulin, lower blood levels of other amino acids which compete with tyrosine for brain uptake) on effects of tyrosine, dopa, or tryptophan.				
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FINAL TECHNICAL REPORT

AFOSR-87-0229

3/30/87 - 3/29/90

Uses of Tyrosine in Foods to Amplify Catecholamine Release

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Research in my laboratory that was all or in part supported by AFOSR during the period 1987-1990 (Grant # AFOSR-87-0229) generated the following publications, which are grouped according to their content and described briefly below. (It should be noted that acknowledgement of AFOSR support is missing from some of them, because some journals - like Scientific American - do not, as a matter of policy, list acknowledgements.)

#### Control by Tyrosine Levels of Catecholamine Synthesis & Release:

Milner, J.D. and Wurtman, R.J.

Commentary: Catecholamine synthesis: Physiological coupling to precursor supply. Biochem. Pharmacol., 35:875-881, 1986.

Milner, J.D., Irie, K., and Wurtman, R.J.

Effects of phenylalanine on the release of endogenous dopamine from rat striatal slices. J. Neurochem. 47:1444-1448, 1986.

Milner, J.D. and Wurtman, R.J.

Tyrosine availability: A presynaptic factor controlling catecholamine release. In: Molecular Mechanisms of Neuronal Responsiveness (Y.H. Ehrlich, R.H. Lenox, E. Kornecki, and W.O. Berry, Eds.) Series: Advances in Experimental Medicine and Biology. Plenum Press: New York and London, 1987, pp.211-221.

Milner, J.D., Reinstein, D.K. and Wurtman, R.J.

Dopamine synthesis in rat striatum: Mobilization of tyrosine from non-dopaminergic cells. Experientia 43(10):1109, 1987.

Irie, K. and Wurtman, R.J.

Release of norepinephrine from rat hypothalamic slices: effects of desipramine and tyrosine. Brain Research 423:391-394, 1987.

Acworth, I.N., During, M.J. and Wurtman, R.J.

Tyrosine: effects on catecholamine release, Brain Research Bulletin 21:473-477, 1988.

#### Effect of Tyrosine on Maintenance of Blood Pressure

Conlay, L.A., Maher, T.J. and Wurtman, R.J.

Spinal cord noradrenergic neurons are activated in hypotension. Brain Research, 375, no.1: 210-213, 1986.

Conlay, L.A., Maher, T.J., Roberts, C.H., and Wurtman, R.J.

Effects of hemorrhagic hypotension on tyrosine concentrations in rat spinal cord and plasma. Neurochem. Intl. 12(3):291-295, 1988.

#### Effects of Other Circulating Nutrients on Maintenance of Blood Pressure

Conlay, L. and Wurtman, R.J.

Endogenous adenosine and hemorrhagic shock: effects of caffeine administration or caffeine withdrawal. Proc. Nat. Acad. Sci., 85:4483-4485, 1988.

Conlay, L.A., Maher, T.J. and Wurtman, R.J.  
 Alanine increases blood pressure during hypotention.  
Pharmacol. & Toxicol. 66:415-416, 1990.

#### Use of In Vivo Microdialysis to Examine Effects of Tyrosine on Neurotransmitters

During, M., Acworth, I.N. and Wurtman, R.J.  
 Effects of systemic tyrosine on dopamine release from rat striatum and nucleus accumbens. Brain Res. 452:378-380, 1988.

During, M.J., Acworth, I.N. and Wurtman, R.J.  
 Phenylalanine administration influences dopamine release in the rat's corpus striatum. Neurosci. Letters 93:91-95, 1988.

During, M.J., Acworth, I.N. and Wurtman, R.J.  
 Dopamine release in rat striatum: Physiological coupling to tyrosine supply. J. Neurochem. 52:1449-1454, 1989.

#### Effects of Tyrosyl- or TRH-Derived Dipeptides on Catecholaminergic Neurotransmission

Maher, T.J., Kiritsy, P.J., Moya-Huff, F.A., Casacci, F., DeMarchi, F. and Wurtman, R.J.  
 Use of parenteral dipeptides to increase serum tyrosine levels and to enhance catecholamine-mediated neurotransmission. J. Pharm. Sci. 79(8):685-687, 1990.

Kreutz, M.R., Acworth, I.N., Lehnert, H. and Wurtman, R.J.  
 Systemic administration of thyrotropin-releasing hormone enhances striatal dopamine release in vivo. Brain Research (in press).

#### Effects of Exercise on Circulating Nutrients

Conlay, L., Wurtman, R.J., Maher, T.J., Lopez-Coviella, I., Blusztajn, J.K., Vacanti, C.A., Logue, M., During, M., Caballero, B. and Evoniuk, G.  
 Effects of running the Boston Marathon on plasma concentrations of large neutral amino acids in human subjects. J. Neur. Trans. 76: No. 1, 65-71, 1989.

#### Circadian Activity Rhythms: Effects of Age

Lieberman, Harris R. and Wurtman, Judith J., Circadian rhythms of activity in healthy young and elderly humans. Neurobiol. of Aging 10:259-265, 1989.

#### Retinal Dopamine and Tyrosine

Godley, B.F. and Wurtman, R.J. Release of endogenous dopamine from the superfused rabbit retina in vitro: Effect of light stimulation. Brain Research 452:393-395, 1988.

Godley, B.F., Dodd, R.L., Chang, A.C., Mauron, C. and Wurtman, R.J.  
Inhibition by melatonin of dopamine synthesis in and release from superfused rabbit retina. (In preparation).

#### Interactions of Levodopa and Dietary Carbohydrates

Wurtman, R.J., Caballero, B. and Salzman, E.  
Facilitation of levodopa-induced dyskinesias by dietary carbohydrates. New Eng. J. Med. 319:1288-1289, 1988.

#### Tryptophan Availability, Carbohydrate Intake, & Serotonin Release

Schaechter, J. and Wurtman, R.J.  
Tryptophan availability modulates serotonin release from rat hypothalamic slices. J. Neurochem. 53(6):1925-1933, 1989.

Schaechter, J.D. and Wurtman, R.J.  
Effect of chronic d-fenfluramine administration on rat hypothalamic serotonin levels and release. Life Sci. 44:265-271, 1989.

Schaechter, J.D., LaFerrere, B. and Wurtman, R.J.  
Effect of chronic d-fenfluramine administration on rat brain serotonin levels and release, pp. 609-613. In: R. Paoletti et al. (eds.) "Serotonin: From Cell Biology to Pharmacology & Therapeutics" Kluwer Academic Publishers, Dordrecht, Boston and London: 1990.

Schaechter, J.D. and Wurtman, R.J.  
Serotonin release varies with brain tryptophan levels  
Brain Research (in press).

#### Nutrition & Behavior

Wurtman, R.J.  
Carbohydrates and Depression. Sci. American, Jan. '89, pp.68-75.

Kaye, W.H., Gwirtsman, H.E., Brewerton, T.D., George, T.D., and Wurtman, R.J.  
Bingeing behavior and plasma amino acids: a possible involvement of brain serotonin in bulimia nervosa.  
Psychiat. Res. 23:31-43, 1988.

#### Review Articles

Wurtman, R.J.  
Ways that foods can affect the brain. Nutrition Reviews,  
"Diet & Behavior: A Multidisciplinary Evaluation, 44:2-6, 1986.

Wurtman, R.J.  
Circulating nutrients and neurotransmitter synthesis.  
J. appl. Nutr. 39(1):7-28, 1987.

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Nutrients affecting brain composition and behavior. Integr. Psychiat. 5:226-257, 1987.

Wurtman, R.J. Effects of their nutrient precursors on the synthesis and release of serotonin, the catecholamines, and acetylcholine: implications for behavioral disorders. Clin. Neuropharm. 9/S4:506-507, 1986.

Wurtman, R.J.  
Effects of dietary amino acids, carbohydrates and choline on neurotransmitter synthesis. Mt. Sinai Journal of Medicine 55: 75-86, 1988

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Effects of their nutrient precursors on the synthesis and release of serotonin, the catecholamines, and acetylcholine: implications for behavioral disorders. Clin. Neuropharm. 11, suppl. 1, S187-193, 1988.

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Processes that couple amino acid availability to neurotransmitter synthesis and release. In: Amino Acid Availability and Brain Function in Health and Disease, G. Huether (ed.) NATO ASI Series; H: Cell Biology. Springer Verlag, 1988, pp.117-136.

Wurtman, R.J.  
Presynaptic control of the release of amine neurotransmitters by precursor levels. NIPS (Am. Physiol. Soc.) 3:158-163, 1988